Volume 110 Number 1 July 1995

The Journal of
THORACIC
AND
CARDIOVASCULAR
SURGERY

EDITORIAL

HIT, HITT, AND DESULFATOHIRUDIN: LOOK BEFORE YOU LEAP

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Heparin-induced thrombocytopenia and thrombosis (HITT) is an increasingly serious risk of cardiac surgery and one that may cause multiple amputations, stroke, death, and lawsuits. HITT causes thrombocytopenia and also the propensity to produce "white clots" consisting mainly of platelets and fibrin in small and medium-sized arteries rather than veins.[1, 2] The disease, HITT, must be differentiated from heparin-induced thrombocytopenia without thrombosis (HIT), which is usually defined as a 40% to 50% decrease in platelet count in response to heparin in the absence of another explanation.[3, 4] Plasma from patients with HIT and HITT is abnormal and contains a substance that often causes platelet aggregation or serotonin release from normal donor platelets when heparin is added.[4-12] Both HIT and HITT are unrelated to the brief (<2 hours), usually small, decrease in platelet count that occurs directly after injection of some heparin preparations.[2, 4, 13] This transient thrombocytopenia is a direct effect of heparin on platelet sensitivity to soluble agonists and produces momentary aggregation and sequestration without consequences.

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J THORAC CARDIOVASC SURG 1995;110:1-3

0022-5223/95 $3.00 + 0 **12/1/64507**

HIT and HITT may or may not be different manifestations of the same disease and may or may not be partially immunogenic in origin.[4-10, 14, 15] These issues are not yet settled, nor is the mechanism of the disease understood.[4-10, 14] HIT usually develops 5 to 8 days after heparin injection in 3% to 5% of all patients and causes a sharp, profound decrease in platelet count to 50% of preheparin values or less.[3, 4, 15] Laboratory tests may confirm the diagnosis; sensitivity of the test varies and continues to be an issue.[4, 6, 11, 15-17] The risk of HIT after cardiac operations is bleeding, not thrombosis, and the treatment is stoppage of all heparin,[1-4, 15, 17] including that in flushes and "locks."[18] Platelet counts return to the normal range within about 5 days.[3, 4, 14]

For many patients absolutely no clues exist before the operation that HITT will develop. Laboratory tests before heparin is given do not detect either HITT or HIT.[3, 4, 17] No test that predicts the thrombotic complications of HITT is available.[4] Although unusual, devastating complications have developed within 2 or 3 days of the first heparin dose and within hours after a second dose.[1, 4] However, two warning signs should be sought in all patients before cardiac operations: (1) a fall in platelet count to less than 50% of preheparin counts (i.e., HIT)[1, 3, 4, 15, 17] and (2) any past or present venous or arterial thromboembolic complication associated with heparin administration.[3, 4] In those patients who have

had prior heparin exposure, laboratory tests may confirm the diagnosis.[3, 4, 6, 12, 15-17] Until better tests are developed, it is not rational to screen every patient because no test predicts HITT. The patient described by Riess and colleagues, in this issue of the JOURNAL (see page 265), had both warning signs and also had a confirming, positive result from a platelet response test; they alertly heeded the red flags and avoided disaster.

When the possibility of the disease is known before the operation, several strategies have been used successfully to avoid HITT. The prostacyclin analog iloprost (Berlex Laboratories, Inc. Wayne, N.J.) works when used with large infusions of phenylephrine,[19] but unfortunately iloprost is no longer produced. Aggressive plasmapheresis[17] before operation can replace most of the patient's abnormal plasma proteins with donor plasma. Low-molecular-weight heparins generally, but not always, cross-react with platelets[6, 17]; heparinoids are less likely to do so.[17, 20] Aspirin pretreatment has been used successfully.[21] None of these protocols are entirely satisfactory or safe; r-hirudin is probably a better solution, but more experience is needed.

HITT may follow HIT, but the incidence is not known. It is estimated that HITT develops in between 0.3% and 0.4% of patients who receive heparin.[2, 4, 15, 17] When postoperative platelet counts fall below 40% to 50% of preoperative counts, heparin should be stopped and signs of HITT sought. If myocardial infarction or limb ischemia develops, lytic therapy is usually not very effective[3, 17] and is potentially dangerous early after cardiac operations. Surgical thromboembolectomy may help some patients,[1-3, 15, 17] but it often fails because small arteries are usually involved.

HITT and other less serious deficiencies of heparin may eventually retire the drug, but probably not soon. The risk of HIT and HITT may be sooner controlled by the use of safe, effective, reversible platelet inhibitors to produce "platelet anesthesia" during cardiopulmonary bypass.[22] r-Hirudin, used successfully by Dr. Riess and his colleagues, is not an adequate substitute for heparin for routine cardiopulmonary bypass for several reasons. First, cardiopulmonary bypass and cardiac surgery produce a massive thrombotic stimulus and, despite doses of heparin that are two to three times those used to treat deep vein thrombosis, thrombin forms and circulates in every patient.[23, 24] Thrombin is a powerful protease that primarily catalyzes the conversion of fibrinogen to fibrin but also initiates many other reactions including activation of platelets. In simulated extracorporeal perfusion we demonstrated that r-desulfatohirudin (Ki = 23 $_{F}$M) is not as effective as standard heparin in suppressing either thrombin formation or fibrinopeptide A production.[25] The probable reason is that r-hirudin inhibits thrombin only after it is formed and therefore does not prevent thrombin formation. Although heparin works as a catalyst, the second-order rate constant for antithrombin III heparin and thrombin is nearly identical to that of native hirudin with thrombin (Ki = 20 $_{F}$M).[26, 27] Antithrombin III–heparin also inhibits factors Xa and IXa and thus has the advantage of partially preventing thrombin formation. Second, there is no pharmaceutical antidote to r-hirudin; that is, there is no protamine or platelet factor 4 to reverse the anticoagulant effect when it is time to close the wound.

The contribution of Riess and associates is an important one but probably should not be extrapolated to routine cardiopulmonary bypass. Studies with r-hirudin in the dog or pig[28, 29] provide testimonial data but do not elucidate the relevant biochemical mechanisms that must be known before the drug can be considered safe. Before jumping on the r-hirudin bandwagon, look before you leap.

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